Prasugrel hydrochloride

Eli Lilly and Company; and Sankyo Pharma

Prasugrel (CS-747) is being studied in patients with acute coronary syndrome (ACS) [i.e., acute myocardial infarction (MI) or unstable angina], who are to undergo percutaneous coronary intervention (PCI; balloon angioplasty). PCI is a procedure that is used to open a clogged heart artery. In patients with ACS, it was demonstrated that the long-term use of antiplatelet drugs [e.g., acetylsalicylic acid (ASA)] results in a decreased risk of ischemic stroke (IS), MI and cardiovascular death.

In 2006, Eli Lilly plans to file a New Drug Application (NDA) for ACS.

Prasugrel is an investigational oral antiplatelet agent that belongs to the thienopyridine family (e.g., clopidogrel and ticlopidine). It is designed to prevent platelet activation by blocking adenosine diphosphate (ADP) P2Y12 receptors on the platelet surface. Prasugrel is a prodrug with an active metabolite called R-9924, a selective and irreversible antagonist of ADP P2Y12 receptors, which is responsible for the drug’s in vivo actions. Animal studies suggest prasugrel may be more potent than clopidogrel.

The pharmacological management of patients who undergo PCI is based on a combination of antiplatelet drugs, including ASA, clopidogrel (or ticlopidine) and glycoprotein IIb/IIIa inhibitors. Although the use of antiplatelet therapy in this setting is established, a few therapeutic issues are unresolved, including the timing of initial therapy before PCI; the dose, including clopidogrel loading dose; the duration of treatment; and situations, that may require additional administration of glycoprotein IIb/IIIa receptor inhibitors.

Despite improvements in patient care during PCI, therapeutic failure with antiplatelet drugs remains. This may lead to recurrent cardiovascular events, including MI. Clopidogrel resistance, consisting of a decreased antiplatelet effect in some patients, has been demonstrated. It is anticipated that such patients may be at an increased risk of recurrent cardiac events. The mechanisms of platelet resistance are unclear, but may include drug interaction (e.g., for cytochrome P450 isoenzymes), inappropriate dosing, variable conversion to active metabolite, ADP receptor variability and an increased release of ADP. These limitations prompted the development of agents such as prasugrel.

There is no information on the price of prasugrel, because it is not marketed in any country.
Emerging Drug List

PRASUGREL FOR PATIENTS WITH ACUTE CORONARY SYNDROME UNDERGOING BALLOON ANGIOPLASTY

Evidence: Preliminary clinical findings are available from the Joint Utilization of Medication to Block Platelets Optimally trial, a study coordinated by the Thrombolysis in Myocardial Infarction study group (JUMBO-TIMI 26). This study was a dose-finding (phase II), double-blinded randomized controlled trial, that was carried out in centres throughout Canada and the US. A total of 904 patients, who underwent elective or urgent PCI with coronary stenting, were randomized to receive one of three doses of prasugrel (40 mg loading, 7.5 mg/day maintenance; 60 mg loading, 10 mg/day maintenance; or 60 mg loading, 15 mg/day maintenance) or clopidogrel (300 mg loading, 75 mg/day maintenance). The antiplatelet therapy was given immediately before or after the procedure; and continued for 30 days.

The primary endpoint was safety [i.e., bleeding other than with coronary artery bypass grafting (CABG) at 30 days]. The secondary endpoint was efficacy, which included the combined rate of major adverse cardiac events (MACE) defined as death; target vessel revascularization (TVR) or target vessel occlusion (TVO); MI; stroke; recurrent ischemia; and individual components of MACE at 30 days. The results of this trial were presented in 2004 at the European Society of Cardiology Congress held in Munich, Germany; and are available on the society’s web site (Table 1).2

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Clopidogrel n=254</th>
<th>Prasugrel n=650</th>
<th>Relative Risk (95% CI)</th>
<th>Risk Difference (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benefits (from cardiovascular events)</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac death</td>
<td>0</td>
<td>3 (0.5%)</td>
<td>2.74 (0.14 to 52.9)</td>
<td>0% (–1 to 0)</td>
<td>0.56</td>
</tr>
<tr>
<td>MI</td>
<td>20 (7.9%)</td>
<td>37 (5.7%)</td>
<td>0.72 (0.43 to 1.22)</td>
<td>–2% (–6 to 2)</td>
<td>0.23</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>3 (0.5%)</td>
<td>2.74 (0.14 to 52.9)</td>
<td>0% (–1 to 0)</td>
<td>0.56</td>
</tr>
<tr>
<td>TVR/TVO</td>
<td>6 (2.4%)</td>
<td>4 (0.6%)</td>
<td>0.26 (0.07 to 0.92)</td>
<td>–2% (–4 to 0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Re-ischemia</td>
<td>9 (3.5%)</td>
<td>11 (1.7%)</td>
<td>0.48 (0.2 to 1.14)</td>
<td>–2% (–4 to 1)</td>
<td>0.09</td>
</tr>
<tr>
<td>All MACE†</td>
<td>24 (9.4%)</td>
<td>47 (7.2%)</td>
<td>0.77 (0.48 to 1.22)</td>
<td>–2% (–6 to 2)</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Harms (from bleeding)</strong>‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significant Bleeding (major+minor TIMI)</td>
<td>3 (1.2%)</td>
<td>11 (1.7%)</td>
<td>1.43 (0.4 to 5.09)</td>
<td>1% (–1 to 2)</td>
<td>0.77</td>
</tr>
<tr>
<td>Major TIMI</td>
<td>2 (0.8%)</td>
<td>3 (0.5%)</td>
<td>0.59 (0.1 to 3.49)</td>
<td>0% (–2 to 1)</td>
<td>0.62</td>
</tr>
<tr>
<td>All bleeding</td>
<td>9 (3.6%)</td>
<td>27 (4.1%)</td>
<td>1.17 (0.56 to 2.46)</td>
<td>1% (–2 to 3)</td>
<td>0.54</td>
</tr>
</tbody>
</table>

*Primary endpoint; †secondary endpoint; ‡not mutually exclusive; major TIMI is ≥5 g Hb decrease; minor TIMI is ≥3 g to 5 g Hb decrease; Hb=hemoglobin; MACE=major adverse cardiac events; MI=myocardial infarction; TIMI=thrombolysis in myocardial infarction; TVR/TVO=target vessel revascularization or target vessel occlusion
A lower percentage of MACE occurred among the 650 patients who were assigned to one of three doses of prasugrel, compared with the 254 patients assigned to receive clopidogrel (7.2% versus 9.4%), but this difference did not reach statistical significance (p=0.31). Among those who suffered MI during the trial, 7.9% were treated with clopidogrel; and 5.7% with prasugrel. This difference also did not reach statistical significance. The lowest rate of cardiac events occurred in patients who received the highest dose of prasugrel (15 mg/day). The only statistically significant difference between prasugrel and clopidogrel was for TVR/TVO, with events occurring in 0.6% of the combined prasugrel group, compared with 2.4% of the clopidogrel group (relative risk reduction of 74%, p=0.03). The results of this exploratory trial suggest that prasugrel is at least as effective as clopidogrel in patients undergoing PCI. The results of JUMBO-TIMI 26 prompted the start of a larger trial (TRITON-TIMI 38) in patients undergoing PCI procedures.

TRITON-TIMI 38 will compare the effects of prasugrel with those of clopidogrel on cardiovascular death; MI; or ischemic stroke in patients with ACS, who are undergoing a PCI with coronary stenting. The study will also assess bleeding, hospitalization for recurrent cardiovascular events and the need for urgent TVR. The study will include 13,000 patients worldwide and it will use the 60 mg loading, 10 mg maintenance dose of prasugrel for a 12-month median duration. People who have had a stroke within the previous three months; those with internal bleeding or a history of a bleeding disorder; or individuals who are at an increased risk of bleeding or who have a medical illness such as liver disease, alcoholism, mental illness or drug dependence, meet the exclusion criteria.

In the JUMBO-TIMI 26 trial, there was no significant difference between prasugrel and clopidogrel with regard to the primary endpoint of significant non-CABG bleeding at 30 days follow-up (Table 1), regardless of the administered prasugrel dose. Similarly, there were no significant differences between the two drugs with regard to the incidence of major TIMI bleeding or the rate of all bleeding episodes at 30 days (Table 1). Although it is not statistically significant, a higher percentage (5.1%) of bleeding episodes (TIMI major + minor + minimal bleeding) was observed at 30 days in the group using 15 mg per day of prasugrel, compared with those using either 7.5 mg per day (3.5%) or 10 mg per day (3.5%). In the study, major bleeds occurred mostly at puncture points and no patient suffered intracranial hemorrhage.

Given the large number of PCI procedures performed (35,000 in Canada during 2000 to 2001), any improvement in the current standard of care would influence the lives of many patients. In the future, other non-thienopyridine ADP receptor inhibitors (e.g., AR-C69931MX) and the antagonists of other platelet targets in development may influence the treatment of patients with ACS, who are undergoing PCI.
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References:


